

Dutch Study Phase IX (Phases I, II, III, IV, V, VI, VII, & VIII & Literature Citations available on request)

This is the ninth part of a personal chronology of my experience implementing the conclusions of the Rotterdam Study (New England Journal of Medicine Nov. 22, 2001). The chronology was started as a memo to my younger brothers and sisters. We have active sporadic Alzheimer's disease in our family history. Our father, his sister and with less assurance, their mother, became clinical victims at their ages of 74-75. Both maternal and fraternal aunts and uncles of my father had AD by 75 years of age. The NIH estimates that this genetic history projects to a 25% risk of AD. The incubation period of AD is likely long, between 4 to eight years, before a clinical diagnosis can be made. I am intent on dodging that bullet and I am pulling out all the stops in that regard. With perseverance I have dodged prostate and colon cancer bullets earlier in my life, and nearing 69 this is just another one. This Alzheimer's challenge is embraced with the joy of discovery and without fear.

Previous reports have illustrated an evolving AD Prevention program, anchored on the use of chronic levels of NSAIDs as reported by the Erasmus Medical Center (EMC) in their Rotterdam Prospective Epidemiological Study. In the last several of these Dutch Study Reports are revealed the intensifying use of anti-oxidant vitamins E & C, the B vitamins, Omega 3 fatty acids from fish, neuron stimulating chemical, Acetyl-L-Carnitine, and a five year history of anti-hypertension therapy. Statins had not been used because LDL is ultra low to start and this was a characteristic of my father's (AD victim) blood chemistry, and also a younger brother's (symptom free). I believe the statins deserve a place in this program. The older and proven drugs Mevacor and Zocor are off patent in several countries. Zocor is now an OTC drug in England. A low dose statin regimen was put in place in early June, starting with low dose 10 mg/day simvastatin (Zocor) and changing to medium dose 20 mg/day lovastatin (Mevacor) in the 45th day.

Turmeric dosing has been again slowly increased to 135 mg/kg-day from June 1, 2004. The curcumin assay of the spice (Raja Foods Inc.) is 2.8%. Dosing on a curcumin basis is now 3.8 mg/kg-day, about three quarters (75%) the metabolic equivalent of 25 mg/kg-day shown to be effective in mice. The whole spice is taken four days per week. Three days per week a 500 mg capsule of concentrated curcumin (WWW.CURMAX.COM) is taken or a dosage of 4.5 mg/kg-day from that source, averaging 4.1 mg/kg-day.

[THE CHRONOLOGY RESUMES]

September 2, 2004 Update at 33 Months:

Today completes 33 months of my Alzheimer's disease Prevention Program (ADPP), following the results of the Rotterdam Study disclosed in NEJM Nov. 21, 2001. NSAID's use has been at 33-80% of the Study's Defined Daily Dose (DDD) using Ibuprofen (908 days) and Naproxen (82 days). The program started with IBP @33→50% DDD, and then switched for a short period to Naproxen @80% DDD. The switch proceeded until July 25th 2002 (eight months into the program) when it was learned that select NSAIDs (Nature 414, Nov. 8, 2001; Koo et al) had been correlated by the Rotterdam Team at Erasmus Medical Center (EMC) and found to contribute disproportionately to their prior statistical correlations. IBP, one of the three NSAIDs, which inhibit a protein-slicing enzyme, which produces a 42 A-Beta (A β) amyloid, an insoluble polypeptide shown to clump into plaque aggregates. Subsequently all NSAID use was returned to Ibuprofen @50→67% DDD. Ibuprofen use had been predominantly at 600 mg/day (50% DDD) except for excursions of 20-38 days at 800 mg/day (67% DDD). The excursions had been terminated for Tinnitus once, and for

foreign travels or extensive domestic trips. The prior periods approximate days at 800 mg were 100.

The immediate period reported on here is the 90 days leading up to the 33-month milestone. The period was marked by continuance of an intensification of the basic program following verification of having inherited an e3, e4 ApoE genotype. The intensification amounted to increasing Ibuprofen to 800 mg/day, now into its 280th consecutive day. (a total of 380 days since program start in November 2001).

Other aspects of the program were intensified earlier as well. Vitamin E (natural) to 1200 IU/day from 800 (synthetic). Continuance of 1000 mg/day of Vitamin C. Folic acid increased from 600 mcg/day to 1000, and in this period raised to 1370. B12 increased from 30 mcg/day to 300 mcg/day and in this period to 525. B6 dropped from 30 mg/day to 22 mg/day. Fish oils increased from 2 grams/day to 5 grams/day using Cod Liver Oil as the additional source of DHA/EPA, with its generous amounts of vitamin D. Expensive Acetyl-L-Carnitine has been continued but at a reduced 300 mg/day level from that used for one year at 500 mg/day.

The family of curves below represents my current assessment of the Rotterdam Study's re-analysis. Study Figure 1 is amended by their own disclosure at Stockholm July 25, 2002 with the 18th month risk reduction attribution to the Trinity of NSAIDs (Ibuprofen, Indomethacin, Sulindac) shown by the Koo/Golde team's to inhibit Abeta 42 enzyme activity. The course of the heavy line is arbitrary except for the origin and 18th month risk reduction Posted by the Erasmus Medical Center for this group. The light curve (original RS finding) now represents the risk reduction of the mildly A β -42 inhibiting NSAIDs (diclofenac and piroxicam) disclosed in a second report by the Koo/Golde teams, and the privileged information I received on the "neutrality" of diclofenac for the whole of the NSAID usage. Diclofenac's effects could be left in or discarded and the risk reduction would not change from the original Figure 1 curve. Diclofenac was the most highly used NSAID (total of 43% of prescriptions, 36% of usage duration) by Rotterdam Study participants and their respective physicians.

To get this weighted conformance of the mildly inhibiting NSAIDs to the original curve, you need to assume that those NSAIDs which show no in-vitro or in-vivo inhibition (like naproxen, 17% of Study weighting) had no contribution to AD risk reduction (flat line A).

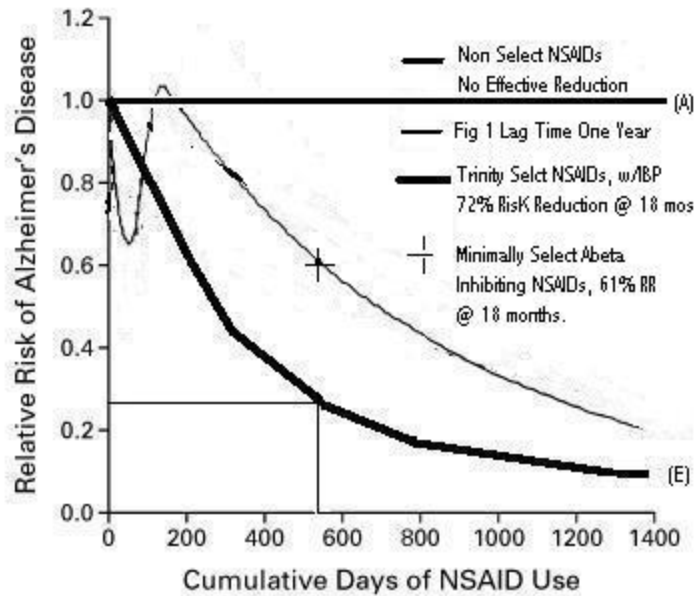
From the curve below, at ca. 900 days of NSAID use, the Alzheimers disease risk is now 16% of what it would have been without the use of A β 42 inhibiting NSAID.

The response to ibuprofen and nutritional supplement intensification has been so favorable that all earlier thoughts of switching NSAIDs will be postponed an additional three months, allowing for the incremental participation of multifunctional curcumin via Turmeric and the start of statin usage via Lovastatin.

The 9th International Conference on AD and related Disorders was attended in Philadelphia this July 17-22. A first hand account from this conference is attached with emphasis on its impact on the ADPP.

The completion of 33 months of this aggressive prevention program without medical complications has been very satisfying. The guidance and co-operation of my physician consultant, and many medical and scientific investigators has been deeply appreciated. A chance to meet some of these face to face in Philadelphia was especially rewarding. Along the way perhaps the best question was asked early on from Dr. Robert W. Griffith who writes a column for Health and Age. He asked whether I was putting all my "eggs in one basket", speaking of its then exclusive emphasis on NSAIDs. There were other eggs and other baskets but they were much smaller elements

than they are now, and I am constantly asking myself how other approaches would fit in. I see a multi component program as necessary now.



Current LGN Rotterdam Study Re-analysis
(A= Assumed) (E= Estimated)

Philadelphia

The Ninth International Conference of Alzheimer's and related Diseases, held in Philadelphia between July 17 and 22, 2004 was an impressive gathering of diverse persons whose careers revolve around this disease. 4500 registrants, from 70 countries attended the (a) day and (b) evening sessions sponsored by the Alzheimer's Association (a) and various pharmaceutical companies (b). The attendees spanned the interests from clinical neurologists, pathologists, radiologists, psychiatrists, and psychologists to scientific disciplines of epidemiologists, biologists, molecular biologists, chemists, and radiation physicists. The forum was the Pennsylvania Convention Center a magnificent facility which easily handled the visitors as they shuffled between concurrent and precisely timed sessions in giant halls, contiguous rooms, and ballrooms. The video and audio technologies of the convention center worked flawlessly, attended to by numerous and competent technicians. The restrooms were never crowded, never had lines, were cleaned every thirty minutes even at the peaks in crowd movements. It is hard to say who performed better, the highly educated presenters-attendees (estimated lowest degree MD, with most having PhD's and combined degrees with post doctoral credentials) the technical and information staff of the center or the Alzheimer's Association staff organizing and administering the event.

With all this dedicated talent intent on unraveling the deeply hidden mysteries of AD one could be quite optimistic for the future, except for a few haunting realizations. (a) This was the ninth conference of its kind, held every two years, so this kind of effort has been building for eighteen years, and (b) there was

no obvious breakthroughs revealed during this conference. Admittedly the progress is impressive, the past tool making in DNA derived analytical techniques, and advances in resolution of computed magnetic resonance and selective electron excitation imaging can readily be seen and admired for the direction they are giving to the search for cause, consequences and prevention of the disease. But other facets of the conference struck this observer as worrisome.

I came slowly to a conclusion that I was participating in a kind of group think that was probably limiting and braking the speed of discovery. This worry developed from my newness to this field. In the earliest sessions I noted the continuous use of acronyms with up to six letters. From my reading of the literature over the last three years I was able to pick up on a majority of the terminology; still a lot was passing by me and crippled my comprehension. Nobody made any effort to explain his terminology. It was expected that everyone knew what these letters meant. I realized that this diversity of education and practice meant that physicians, only modestly introduced to chemistry, and chemists knowing nothing of human anatomy and organ dysfunction could not possibly be bridging all these presentations without any explanations of terminology or existence of a glossary. The Alzheimer's Association had a magnificent program guide and a 650 page densely printed abstract of all the papers and posters, and a CD of the same abstracts all available on day one. One omission was crying out to be included in this 186 page program guide and that was a glossary of terms. Probably if one were available it would be the most referred to of all its pages.

This proved so bothersome to me I started to review what acronyms do to the thought process. They short circuit thinking. Take any simple acronym you use all the time, then say the words slowly, with consideration of what these words mean. You see almost right away that words mean something, they are important. The letters representing these words say almost nothing and short circuit the whole meaning of what is being said. I saw right away that it applies to my own fields of industrial chemistry and chemical engineering. In this conference PET meant positron emission tomography, and there were adjectives of FDG before PET, as in FDG-PET being thrown around in the cranial imaging sessions. In my field PET stands for polyethylene terephthalate as in a resin for a carbonated beverage container or a polyester fiber. The words mean something profound, whereas the letters mean almost nothing, yet they allow participants in an activity to act and sound knowledgeable when in fact nothing fundamental is really being understood. Try it with CIA and FBI as an exercise. You might readily see the problem.

We witnessed this most recently in a business school inspired analytical tool for securities valuation. EBITDA! In the 1990's if you attended any meeting on business valuation, corporate finance, stock prices, and industrial growth and did not witness endless use of this term you must have been a municipal bond investor. I got so disgusted with its use and abuse that when I had the option, I left the room in mock revulsion when it first reared its ugly head. You could make light of the nonsense that sprang from this but it pervaded everything, from investment banks on Wall Street to the backwaters of a Sumatra palm oil processing plant, up for sale. Said slowly with thought it was describing a Kool Aid Stand concept of business like your mother might have encouraged you to operate at age 8. For ten years this concept ran the world of business and nearly led to a second Great Depression. I sensed this group think in Philadelphia. A kind of Parroting, with consensus, on 'Polly Wants a Cracker'. I hope I am wrong.

Viewed by this observer the AD conference was a grand display of the steadily and impressively building of the tools and techniques of a specialized science. The tools and techniques du jour are brain imaging with high resolution magnetic resonance imaging (MRI) and PET amplified by the new technique of

amyloid seeking, then clearing radionuclides. These join ELISA and Western Blot quantitative micro analyses of proteins, Transgenic models of human plaque, then tau replicating mammals, A β 42 vaccines inducing antibodies, all in the search for a single disease cure. What is needed to this observer's mind is a unifying discipline to pull all these scientific findings together. It was not the sciences of rocket propulsion and celestial mechanics that landed men on the moon in a decade, or the science of nuclear physics that built the plutonium production and uranium isotope separation plants at Hanford, Washington, and Oak Ridge, Tennessee in thirty months. Until Bioengineering comes into its own, all this virtuosity may lead to little but discordant sounds across the spectrum of neurological disorders.

Related, but only superficially, was the complete absence of any references to sporadically mentioned surgical techniques applicable to Alzheimer's disease. From time to time the press has mentioned that this or that surgeon has implanted a shunt into the brain drawing off controlled quantities of cerebral spinal fluid (CSF) containing A β oligomers, thus preventing their supersaturation and deposition as plaque. Perhaps the surgeons, being only talented mechanics, did not feel at home there.

Prevention Progress

So how did the prevention strategies embodied in my AD Prevention Program (ADPP) stand up under the collective examinations of the 9th International Conference on Alzheimer's disease?

Nonsteroidal Anti-Inflammatories (NSAIDs):

As previous readers will remember the cornerstone of the Dutch Study (ADPP) program is the findings of the Prospective Epidemiological Rotterdam Study by the Erasmus Medical Center (EMC) of that City. To my great disappointment EMC presented no updated findings on NSAIDs at this conference. Particularly disturbing was Dr. Monique Breteler, chief epidemiologist of that institution, co-chaired one of the early sessions on epidemiology where Dr. Peter Zandi, a John's Hopkins researcher, of the Cache county (Utah) team presented a quasi meta or pooled findings from his and three other legacy studies (not including Rotterdam) which led to a new conclusion that naproxen had the same risk reduction power as ibuprofen in terms of AD, about a 40% reduction.

On its face this re-analysis refuted the work of the Golde/Koo teams which postulated, based on in-vitro and in-vivo transgenic mice experiments, that select NSAIDs inhibit an enzyme which slices Abeta amyloid into 42 peptide chains, without shutting down 38-40 chain processing. Dr. Breteler is sitting on additional data from 1998 when their suburban Ommoord, Netherlands cohort was last assessed. At the end of 2003 there is five (5) more years of data on this 7000 person cohort, many now of which have been on NSAIDs for much longer than the 24 month period which seemed so critical in achieving a full 80% reduction in risk when reported in November 2001. In July 2002, for the 8th International Conference, at Stockholm, Dr. Breteler reported on a reanalysis of their earlier data which suggested that most of their measured risk reduction followed the findings of Golde/Koo respecting NSAID selectivity.

While I believe the Rotterdam study is by far and away the best epidemiological work, to see its representative sit mum like a sphinx during a lively discussion of where the truth might be, is extremely frustrating. The very expensive and important ADAPT (Alzheimer's Disease, Anti-Inflammatory Prevention Trial) is underway, with Celebrex and Naproxen as the candidate NSAIDs, neither of which exhibit Abeta 42 enzyme inhibition. Attempts to graft an ibuprofen "Arm" onto that trial have been

rebuffed by NIH. If neither of these Cox 2 or the Cox 1 NSAIDs chosen produce an AD reduction risk in the ADAPT work we will have lost about 5-7 years and will have discredited the most promising class of prevention compounds. There is a chorus singing a song that it does not matter which NSAID you use. Their findings are based on (a) this questionable work in the Cache County Study where the important data on NSAID dosage was not even reliably gathered or presented, or (b) the findings are based on the equivalent performance of mice re-locating resting platforms in a water maze.

I spoke to Dr. Breteler with whom I have corresponded (mostly one way mailing of my reports). She recalled the reports and defended her silence by saying they are going to do their formal update at the end of 2004 and expect to be in a position to publish their findings in mid to the fall of 2005. She indicated they want to be very careful in their analysis and not make a mistake like Hormone Replacement Therapy (HRT) as revealed in the Woman's Health Trials with Progesten and Estrogen. Dr. Breteler did acknowledge that their data base is substantially greater now with the added years and additional persons flowing into the cohort. She expressed the view that the 2005 findings would be much stronger statistically respecting risk reduction as affected by all of the factors reported in 2001 including NSAID type, duration, APOE, smoking, gender, etc.

Is statistical purity alone determining disclosure? Is ADAPT going to be threatened? Stay tuned for this exciting conclusion.

Antioxidants:

The next aspect of the ADPP is the lessening of oxidative damage in brain cells through the use of an antioxidant package. The leading component of the package is megadose vitamin E, supported by megadose vitamin C. Vitamin E is a long lived, lipid soluble antioxidant which circulates in the bloodstream, and is quite efficient at oxidizing itself in the presence of free radicals of oxygen donor species. It readily regenerates itself by handing off the oxidized ions at its extended aliphatic branch to vitamin C a short lived, water soluble oxygen scavenger. The d isomer form of this optical isomer has about 1.5 times the bioavailability as the mixed dl isomer characteristic of synthetic vitamin E. I use a total of 1200 mg/day of the d isomer spaced 5 hours apart, taking 500 mg of vitamin C with the morning and evening portions. To these core elements I have added either the 2.8% curcumin containing spice Turmeric or its concentrated curcumin active ingredient in capsule form at the equivalent of 450 mg/day. Curcumin and Turmeric are both powerful antioxidants as is readily revealed when compounding them with water in the kitchen, and spilling same on spousal cleaned countertops.

This is an antioxidant package I believe has a chance of stopping oxidative damage in the brain. This is orchestrated to work with the NSAIDs which reduce the inflammatory excursions in the brain reporting as headaches, or head bump swelling in everyday living and microscopically and localized at insoluble amyloid cites within the aging brain. With temperature excursions accompanying injury or fever it is most likely that oxidative damage can accelerate. Each of the above ADPP premises to this strategy is supported by independent experiments in cell culture and/or transgenic mouse experiments and/or epidemiological human studies.

Dr. Ronald Peterson of the Mayo Clinic reported on the results of the Alzheimer's disease Cooperative Study trial to measure the further progression of patients who had already progressed to Mild Cognitive Impairment (MCI). The 769 patient, 69 medical center trial pitted 2000 mg/day Vitamin E against

donepezil (Aricept) the cholinesterase inhibitor, and a placebo. Over 50% of the patients had the APOE-4 genotype and overall progression to clinical dementia was 13% per year, aggregating 195 patients. Drop out occurred at a 12% per year rate aggregating 311 patients. In three years the progression was the same for all groups. The vitamin E group's progression closely followed the placebo group. The donepezil group had an interval from 9 months to 16 months where progression slowed significantly, relative to placebo, but then progression accelerated in the subsequent 21 months, ending at the same degree, at 36 month trial end. The gist of this trial was a nod to donepezil as a MCI treatment to delay institutionalization and ease patient care at home for a certain period. This trial was a disappointment for advocates of megadose vitamin E as an antioxidant for prevention.

Each trial subject took a daily multivitamin which typically has 60 mg vitamin C, and vitamins B12, B6, and folic acid all at 100% of their respective recommended daily values (RDA). The trial used Roche Pharmaceuticals dl synthetic alpha tocopherol mixture which has 2/3 the bioavailability of the d isomer. The antioxidant package consisted of one compromised component. The l (levo) isomer subjects the patients to the same GI bleeding risk as the d isomer but contributes little or nothing to the antioxidant role in cells. Ironically the Cache County Study reported earlier this year in Archives of Neurology (volume 61 pp 82-88, 2004) that their retrospective epidemiological work showed that vitamins C&E when taken alone produced measurable but non significant AD risk lowering but when take together, as substantial supplements, Vitamin E and C had a significant AD risk reduction or rather lowered odds ratios of incident AD when compared to persons taking no vitamin supplements. Cache County considered daily intake of 400 IU or more of E and 500mg or more of C to be representative of significant supplemented quantities. The Mayo managed trial drop out total was back calculated from the abstracted paper's disclosure of the annual rate. Subtracting this from the total patients at the start, and calculating the converters from MCI to AD and other dementias from that remainder, as a check, yields 200, approximately as reported. It looks like the 40% drop out rate in three years would require the most explanation. You have to wonder why an average patient load of 11 at each center would drop to 7 in a trial. Four (4) drop outs each which presumably were not the most impaired (not yet converters).

I consider the ADPP use of antioxidants, as a package in concert with an NSAID, to be more rational than the reported trial managed by the Mayo Clinic team. The trial seeks to determine the power of an individual agent to affect change in outcomes whereas the ADPP approach is to marshal all well tolerated agents as an ensemble. I will never learn what, if anything, in my program worked. There is some doubt if the hundreds of carefully crafted, NIH funded, Clinical Trials will either.

Vascular Support:

Vitamin Lowering of Homocysteine

A later component of the ADPP has been the vitamin package which supports specific disinflammation in the blood vessels of the cardiovascular system and the brain. One of the hallmarks of Alzheimer's disease is that the brain begins to shrink at a rate four (4) to eight (8) times that of healthy normals in the five years leading up to a clinical diagnosis for victims of Familial Alzheimer's Disease (FAD), and to smoothly accelerate the rate of shrinkage through that period and beyond the diagnosis. This work has been developed with ingenious volumetric MRI work by a group headed by Nick Fox of University College in London in 2001. FAD victims, determined by an inherited genetic mutation, are younger < 55 years of age at diagnosis, than victims of late onset, sporadic AD (> 65).

At Philadelphia a group from the Oregon Health and Science University extended this, serially measuring the increase in brain ventricle (CSF filled voids) volumes in older subjects which later developed cognitive impairment. This work developed that ventricle volumes accelerated smoothly over a seven year (as much as 11 years and as little as 4 years) period prior to diagnosis. It is this accelerating collapse of brain tissue, generally in all of the subunits of the brain, which we are trying to slow or eliminate with the vascular vitamin package. A marker of vascular inflammation is the presence of a protein in the bloodstream, homocysteine. There is a normal increase of homocysteine (tHcy) as we age from levels of 9 μ mol/liter to 15 μ mol/liter. At a level of 14 the risk of AD doubles. A typical level at age 66 would be 11, at age 76 is 12.5, and at 86 homocysteine would be expected to be 14.

There are numerous correlations of homocysteine levels with brain atrophy, notably the Nuns Study examined brains of deceased teaching Nuns whose medical records had been closely followed for years and neurological tests performed as they aged, and related to early life use of written language in an idea dense manner. The high homocysteine level correlated with more severe brain atrophy and lower serum folate levels. Years of coronary vascular disease study have shown that the B vitamins folic acid, 12, and 6 taken at mega dose levels, lowers homocysteine. Folic acid has by far the greatest effect, B12 comes in a strong second and B6's effect is only slight. Taken together at rates 3 to 50 times the minimum daily requirement leads to a 4 μ mol/liter decrease in homocysteine from the 14 level. As yet there is no data showing that AD incidence lowering follows from such a tHcy lowering, but the linkage of atrophy with high homocysteine and the linkage of atrophy with Alzheimer's pathology, years before clinical diagnosis, is evidence enough for me to include, and now increase, the B vitamins in the ADPP.

Folic acid dosing will go from 1028 micrograms/day to 1.37 milligrams/day, a 33% increase, and vitamin B12 will go from 313 micrograms/day to 525 mcg/day, a 68% increase. The unbalanced increase is made to provide a sufficient off set to folic acid which can mask a theoretical B 12 deficiency respecting neuropathy. These two inexpensive B vitamins have performed medical miracles with prevention of tragic neurological birth defects and instant cures of once fatal pernicious anemia and we are continuing to learn of their power. Unlike vitamin E there are no known downsides to mega dosing with these vitamins at dosages three times (3X) my new levels.

Statin Drugs

At the outset of the ADPP one of the reputed agents that might be helpful in preventing Alzheimer's disease were cholesterol lowering statin drugs. A headline study, MIRAGE, headed by Robert C. Green of Boston University in Mid 2002, announced a risk reduction observational analysis of 79% when a 1000 member group with possible or probable AD was compared with 1600 of their relatives and the respective use of cholesterol lowering drugs including statins. These findings followed an earlier study (Archives Neurology v.57, Jan 2000) by Benjamin Wolozin of Loyola University which looked retrospectively at AD statin and hypertension drug use from 57,000 Chicago area hospital patient records and at two large veterans hospitals. This earlier Wolozin work developed that use of lovastatin and pravastatin, two of the oldest statins, exhibited a 69% lower prevalence of AD, while the newer simvastatin exhibited only a non significant 6% reduced prevalence. The latest blockbuster disclosure was made by Dr. Larry Sparks of the Sun Health Research Center (Phoenix) at a Spring 2004 conference in Montreal, that lipitor

(atorvastatin) stopped the progression of 2/3's of the lipitor treated AD patients in a 63 person, one year, trial.

I had viewed these announcements and study findings with a certain skepticism. I have always had low total cholesterol and a LDL (the target for statin therapy) level under 60 mg/dl. Further, the case of AD that I knew the most about, my Father's, also had cholesterol levels under 90 (not including triglycerides divided by 5) and a younger brother has total cholesterol of 105. We have inherited low cholesterol, and LDL level and it seemed that the virtue of statins, if they existed, would not likely apply to me. Still the argument of the statin investigators raised the issue that statin AD prevention benefits were distinct from their cholesterol lowering. Other cholesterol lowering drugs such as niacin showed no AD prevention. With that background the ADPP added simvastatin on June 9th, 2004, at 10 mg/day along with niacin at 500 mg/day, progressed briefly to 20 mg simvastatin, and changed to 20 mg lovastatin July 24th, 2004. The niacin was gradually lowered when it was found that a hot flash which flushed the face with redness occurred about 4 hours after morning dosing with the extended delivery vitamin form. Total cholesterol readings accompanying BCNJ platelet donations in June, July and August showed a sharp drop from 131 to 96 with simvastatin at its low dosage, and a partial return to 114 under lovastatin. A complete lipid profile has yet to be determined.

At the Philadelphia conference the benefits of Statins were put into question by the leadership of the Cache County Study which reviewed their own cohort, that of the Cardiovascular Health Study (CHS) and the Adult Changes in Thought Study (ACT) a total of 6500 participants with 38,000 participant years and 410 AD cases and concluded that results which uniformly showed a statin prevention benefit had a built in bias against attending doctors prescribing statins to persons with cognitive complaints. When statistical adjustments were made to correct for the bias the statin AD prevention risk lowering disappeared.

This was not the first study which questioned the whole statin AD prevention question. A leading Swedish group published (Archives of Neurology, v 61, March 2004) a study of the effects of two statins' effects on the A β 40 and 42 amyloids in blood plasma at the same time the characteristic lipid lowering was underway. It was assumed that statins would reveal at least a hint of altering the levels or the ratio's of these products of brain Amyloid Precursor Protein (APP) metabolism, the former could be called the "good amyloid" and the latter the "bad amyloid" respecting their role in plaque formation and metabolite clearance. Over a 9 month period, and when used at high dosages on patients with high total and LDL cholesterol both the hydrophobic simvastatin and the hydrophilic atorvastatin reduced total cholesterol by 44%. Neither specie of A β Amyloid's were changed in plasma concentration, essentially saying that high dose statins have no effect on amyloid passage from brain to plasma. In a certain sense it confirms a premise that brain cholesterol is generated in brain cells themselves which are largely unaffected by liver enzyme inhibition and the isolation of the blood brain barrier.

At Philadelphia the same Swedish group presented up-to-date findings on these statins's effects on the Cerebral Spinal Fluid (CSF) presence of A β 42, and total Tau which have been previously shown to be sensitive biomarkers for Alzheimer's disease years before a clinical diagnosis can be made. The CSF assays with AD patients on low dose simvastatin for a year do not show any signs of a significant positive change (characteristic of disease moderation) over baseline concentration, and in fact show a non significant drift to lower A β 42 concentrations in 19 patients.

The Mayo Clinic disclosed results of following 1000 subjects for 2-12 years and 4000 samples of plasma analyzed for A β 40 and A β 42. They presented a convincing case, in slides only, that the ratio of these two species could be used to predict AD incidence years ahead of clinical diagnosis. If high dose statins have no effect on either polypeptide concentration, and thus ratio in plasma, it is a stretch to imagine a prevention mechanism for statins. The contrast with folic acid and its definitive effect on homocysteine, and the homocysteine link to brain atrophy is stark.

Dr. Robert Green was present at Philadelphia and associated with two oral presentations and four posters. The topics were about genetic influences and vascular brain tributaries. Statins apparently were set aside but not forgotten.

The net upshot of statin use as an AD prevention strategy is a well deserved skepticism. Philadelphia presentations directly and indirectly served to deepen that skepticism. My choice of lovastatin in the ADPP is based on a desire to use a blood/ brain transiting hydrophobic drug, and the price of that drug. Lovastatin has had years of exposure and is perhaps the safest of the statins on the basis of the time and extent of use, and is now off patent on a world wide basis and is lower in price as a consequence.

Omega 3 Fatty Acids

Omega 3 Fatty acids were originally a part of the ADPP by virtue of late 1990's advice received from old friends on the virtue of flaxseed oil. Some of these omega 6 oils convert to DHA and EPA a hexanoic and pentanoic omega 3 constituent, but with a loss in yield on conversion. The omega 3 oils are directly available from fish and numerous studies endorse their use for maintaining good health in the whole vascular system including the brain. The ADPP includes whole body fish oils 2 grams per day, and cod liver oil 5 grams per day, the source of about 700 mg/day of DHA and 1000 mg/day of EPA. It is the DHA content that is the greater value.

Dr. Greg Cole of UCLA presented a paper about central nervous system (CNS) insulin signaling, actin assembly and synaptic plasticity in a AD mouse model. I understood very little of this presentation except that DHA deprived mice did very poorly in the Morris Water Maze. In summing up his presentation Dr. Cole advised, "take buckets of fish oil".

It is Cole's group that is vigorously exploring the A β amyloid inhibition of Turmeric derived Curcumin, found by them to have the same potency as ibuprofen, at modest dosages. Curcumin then has similar anti inflammatory properties as NSAIDs as well as being a powerful antioxidant. Curcumin is attracted to existing amyloid deposits and appears to help mobilize through solvation and clearance. I could advise its use in place of ibuprofen for anyone who has or develops a GI problem with NSAID prevention therapy. A small trial is being planned for AD therapy applications for Curcumin.

Finally, a conference devoted exclusively to AD Prevention, sponsored by the Alzheimer's Association, is scheduled for Summer 2005 in Washington DC. What a platform for the Rotterdam Study!

